

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/012503 A3

- (51) International Patent Classification⁷: C12N 5/08, A61K 35/12, A61P 21/00
- (21) International Application Number: PCT/EP2003/009008
- (22) International Filing Date: 30 July 2003 (30.07.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/399,745 30 July 2002 (30.07.2002) US
- (71) Applicant (for all designated States except US): TIGENIX N.V. [BE/BE]; Technologielaan 3, B-3001 Leuven (BE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): DE BARI, Cosimo [IT/GB]; 46, Mays Hills Road, Bromley, Kent BR2 0HT (GB). LUYTEN, Frank [BE/BE]; Baron d'Huartlaan 193, B-1950 Kraainem (BE). DELL'ACCIO, Francesco [IT/GB]; 46, Mays Hills Road, Bromley, Kent BR2 0HT (GB).
- (74) Agents: HERTOGHE, Kris et al.; Bird Goën & Co., Klein Dalenstraat 42 A, B-3020 Winksele (BE).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

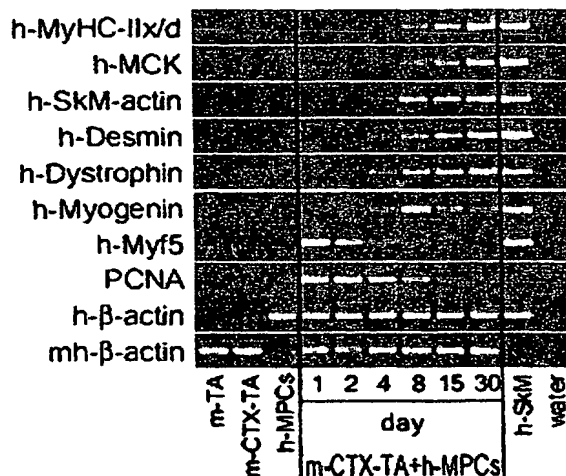
Published:

— with international search report

(88) Date of publication of the international search report:
9 December 2004

[Continued on next page]

(54) Title: COMPOSITIONS COMPRISING MUSCLE PROGENITOR CELLS AND USES THEREOF



(57) Abstract: The present invention shows the *in vivo* myogenic differentiation of muscle progenitor cells (MPCs), being derived from joint tissue, in a mouse model of skeletal muscle regeneration. MPCs participated in the regeneration process by long-term persistence and contribution to the compartment of myonuclei and the pool of functional satellite cells. When injected into dystrophic muscles of immunosuppressed mdx mice, human MPCs restored dystrophin in some fibers, and rescued the expression of mouse mechano-growth factor. In addition, the human MPCs derived from synovial membrane were injected into infarcted myocardial muscle. The MPCs engrafted successfully, underwent proliferation and differentiation leading to functional recovery and maintenance of the cardiac muscle. MPCs represent an alternative source of myogenic cells in therapeutic approaches for postnatal skeletal and cardiac muscle repair.

BEST AVAILABLE COPY

WO 2004/012503 A3

WO 2004/012503 A3



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/09008

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N5/08 A61K35/12 A61P21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DE BARI ET AL: "Multipotent mesenchymal stem cells from adult human synovial membrane"</p> <p>ARTHRITIS AND RHEUMATISM, vol. 44, no. 8, 2001, pages 1928-1942, XP002266867</p> <p>cited in the application</p> <p>page 1929, left-hand column, paragraph 3 - right-hand column, paragraph 2</p> <p>page 1936, right-hand column, paragraph 2 - page 1937, left-hand column, paragraph 1</p> <p>page 1937; figure 5</p> <p>page 1940, left-hand column, paragraph 5 - right-hand column, paragraph 1</p> <p>-----</p> <p>-/--</p>	<p>1-27,</p> <p>32-35</p>

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

14 January 2004

Date of mailing of the international search report

10.05.2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Sitch, W

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/09008

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DE BARI C ET AL: "Human synovial membrane-derived mesenchymal stem cells for skeletal muscle repair" ONCOLOGY RESEARCH, vol. 12, no. 6-7, 2001, page 284, XP008026328 2001 Millennium International Conference of Molecular and Tumor Biology; Santorini, Greece; September 02-07, 2001 ISSN: 0965-0407 abstract 31</p>	1-27, 32-35
X	<p>----- DE BARI C ET AL: "Human mesenchymal stem cells from synovial membrane contribute to skeletal muscle repair in vivo" CLINICAL RHEUMATOLOGY, vol. 20, no. 5, 2001, page 400, XP001184115 5th Belgian Congress on Rheumatology; Hasselt, Belgium; September 27-29, 2001 ISSN: 0770-3198 abstract RA11</p>	1-27, 32-35
P,X	<p>----- DE BARI COSIMO ET AL: "Skeletal muscle repair by adult human mesenchymal stem cells from synovial membrane." JOURNAL OF CELL BIOLOGY, vol. 160, no. 6, 17 March 2003 (2003-03-17), pages 909-918, XP002266868 ISSN: 0021-9525 page 909 abstract</p>	1-27, 32-35
P,X	<p>----- DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 2003 (2003-05), VANDENABEELE F ET AL: "Morphological and immunocytochemical characterization of cultured fibroblast-like cells derived from adult human synovial membrane." XP002266869 Database accession no. PREV200300404606 abstract & ARCHIVES OF HISTOLOGY AND CYTOLOGY, vol. 66, no. 2, May 2003 (2003-05), pages 145-153, ISSN: 0914-9465</p> <p>-----</p>	1-27, 32-35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/09008

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 25-27, 32, 33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-27, 32-35

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 25-27, 32, 33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-27, 32-35

Compositions, in particular pharmaceutical compositions, comprising the joint tissue derived muscle precursor / progenitor cell population; use thereof in the manufacture of pharmaceutical compositions, therapeutic uses thereof

2. claims: 28-31

Method of selecting muscle precursor cells via contacting a joint derived cell population with a binding substance for various markers of the cell population
